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(54) Title: TECHNETIUM-99m LABELED POLYPEPTIDES FOR IMAGING

(57) Abstract

The invention relates to radiolabeled imaging of a mammalian body. The invention in particular provides for reagents labeled with technetium-99m for such imaging. The invention provides peptides which bind technetium-99m and which can be targeted to specific sites within a mammalian body.

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TECHNETIUM-99m LABELED POLYPEPTIDES FOR IMAGING

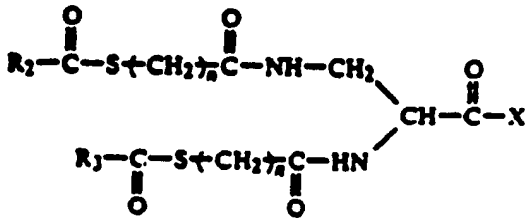
BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to radiodiagnostic reagents and, more particularly, to polypeptides useful for producing technetium (Tc-99m) labeled radiodiagnostic agents. The invention relates to Tc-99m labeled reagents, kits for making such reagents, and methods for using such reagents.

Description of the Prior Art

U.S. Patent No. 4,861,869 (Nicolotti) describes coupling agents of the formula:

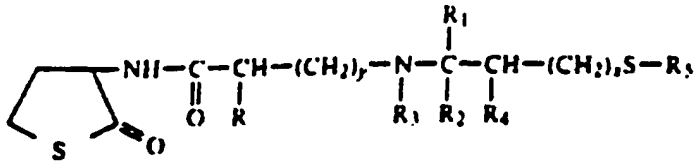


wherein R_2 and R_3 are the same or different and each represents a radical selected from the group consisting of alkyls having from 1 to 6 carbon atoms, aryls having from 6 to 8 carbon atoms and aklaryls having 7 to 9 carbon atoms, any of which can be substituted with one or more hydroxyl, alkoxy, carboxy or sulfonate groups; n is either 1 or 2; and X is an activating group capable of forming an amide bond with an alpha or beta amino group of a biologically useful protein or polypeptide molecule.

U.S. Patent No. 4,861,869 also describes compounds such as S-benzoylmercaptoacetylglyclglyclglycine.

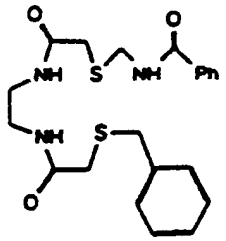
The coupling agents are bound to large peptides such as antibodies or fragments thereof and complexed to Tc-99m.

U.S. Patent Nos. 4,571,430, 4,575,556 and 4,434,151 (Byrne et al.) describe compounds of the formula:



wherein R is hydrogen or lower alkyl, R_1 and R_2 are individually hydrogen or lower alkyl or taken together form oxo; R_3 is an amino protecting group where R_1 and R_2 taken together form oxo; R_4 is hydrogen or lower alkyl; R_5 is hydrogen or a thiol protecting group; and y and z are integers from 0 to 2; which are bifunctional chelating agents and as such can couple radionuclides to terminal amino-containing compounds capable of localizing in an organ or tissue which is desired to be imaged.

Bryson et al., *Inorg. Chem.* 27: 2154-2161 (1988) and *Inorg. Chem.* 29: 2948-2951 (1990), describes thiolate ligands for complexing with technetium of the formula:



European Patent Application No. 86100360.6, filed January 13, 1986, describes dithio, diamino, or diamidocarboylic acids or amine complexes useful for making technetium imaging agents.

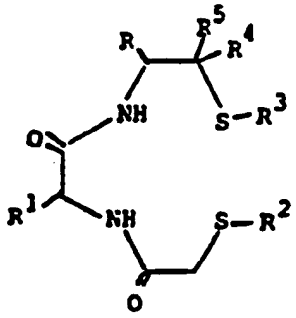
Other references of interest include Khaw et al., *J. Nucl. Med.* 23: 1011 (1982); Rhodes, B.A., *Sem. Nucl. Med.* 4: 281 (1974); Davidson et al., *Inorg. Chem.* 20: 1629 (1981); and Byrne and Tolman, *J. Nucl. Med.*

24: 126 (1983). *See* particularly Fritzberg et al., *J. Nucl. Med.* 23: 592 (1982); Fritzberg et al., *ibid.* 23: 17 (1982), for descriptions of mercaptoacetyl derivatives of ethylene diamine carboxylic acid derivates. *See also* U.S. Patent Nos. 4,434,151, 4,444,690 and 4,472,509.

European Patent Application 88104755.9 describes various S-protected mercaptoacetylglycylglycine chelating groups bound to large proteins such as antibodies.

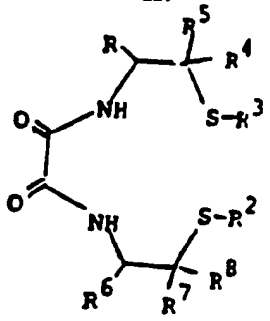
European Patent Application 84109831.2 describes technetium complexes of compounds of the formula I and II:

I.



and

II.



wherein R and R_6 are each selected from hydrogen, substituted or unsubstituted lower alkyl or -COR where R_9 is selected from hydroxy, substituted or unsubstituted lower alkoxy, substituted or unsubstituted amino, glycine ester, or an activated leaving group; R_1 is selected from hydrogen, or substituted or unsubstituted lower alkyl; R_2 and R_3 are each selected from hydrogen or a thiol protecting group; and R_4, R_5, R_7, and R_8 are each selected from hydrogen or lower alkyl; and salts thereof. These complexes

were used primarily as renal function monitoring agents.

Arginylglycylaspartate (Arg-Gly-Asp *or* RGD) and derivative peptides are known to bind to blood clots (*see* U.S. Patent Nos. 4,792,525, 4,857,508 and 4,578,079) and RGD derivatives have been labeled with technetium as imaging agents, *Journal of Nuclear Medicine* 31, pp. 757, No. 209 (1990).

SUMMARY OF THE INVENTION

The invention encompasses polypeptides for labeling with technetium-99m and imaging target sites within a mammalian body comprising (a) a specific binding polypeptide region which specifically binds to the target site to be imaged, and (b) a technetium binding region of the formula Cp(aa)Cp wherein Cp is a protected cysteine and (aa) is an amino acid and wherein the technetium binding region is covalently bound to the specific binding polypeptide region. The invention includes technetium-99m complexes and methods for using the technetium-99m complexes to image target sites within a mammalian body.

DETAILED DESCRIPTION OF THE INVENTION

The Cp(aa)Cp technetium binding group is covalently linked to the specific binding polypeptide preferably by one or more amino acids, most preferably glycine. Alternatively, the Cp(aa)Cp technetium binding group may be directly covalently linked to the specific binding polypeptide or other covalent linking groups can be used such as bifunctional amino/carboxy compounds which are not naturally-occurring amino acids.

Representative specific binding polypeptide sequences are:

Atherosclerotic Plaque Binding Peptides

YRALVDTLK
RALVDTLK
RALVDTLKFVTQAEGAK
YAKFRETLEDTRDRMY
AKFRETLEDTRDRMY
YAALDLNAVANKIADFEL

Atherosclerotic Plaque Binding Peptides (cont'd.)

AALDLNAVANKIADFEL
YRALVDTLKFVTEQAKGA
RALVDTLKFVTEQAKGA
YRALVDTEFKVKQEAGAK
RALVDTEFKVKQEAGAK
YRALVDTLKFVTQAEGAK

Peptides Targeted to Infections and Atherosclerotic Plaque

VGVAPGVGVAPGVGVAPG
VPGVGVPGVGVPGVGVPGVG
formyl.Nleu.LF.Nleu.YK
formyl MIFL
formyl MLFK
formyl MLFI
formyl MFIL
formyl MFLI
formyl MLIF
formyl MILF
TKPR
VGVAPG
formyl MLF

Thrombus

NDGDFEEIPEEYLQ
NDGDFEEIPEEY(SO_3Na)LQ
GPRG

Platelets

D-Phe.PRPGGGGNGDFEEIPEEYL
RRRRRRRRRGDV
PLYKKIIKKLLES
RGD
RGDS

Infection and Atherosclerotic Plaque

YIGSR
CH_2CO.YIGSRC

Alzheimers Disease (Amyloid Plaque)

EKPLQNFTLSFR

[Single letter abbreviations for amino acids can be found in G. Zubay, Biochemistry (2d ed.), 1988, (MacMillan Publishing: New York), p. 33.]

In the Cp(aa)Cp, the Cp is a protected cysteine where the S-protecting groups are the same or different and may be but not limited to:

$-CH_2$-aryl (aryl is phenyl or alkyl or alkyloxy substituted phenyl);

$-CH-(aryl)_2$, (aryl is phenyl or alkyl or alkyloxy substituted phenyl);

$-C-(aryl)_3$, (aryl is phenyl or alkyl or alkyloxy substituted phenyl);

$-CH_2$-(4-methoxyphenyl);

-CH-(4-pyridyl)$(phenyl)_2$;

$-C(CH_3)_3$

-9-phenylfluorenyl;

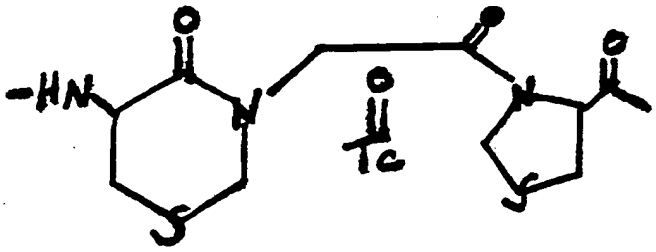
$-CH_2NHCOR$ (R is unsubstituted or substituted alkyl or aryl);

$-CH_2$-NHCOOR (R is unsubstituted or substituted alkyl or aryl);

-CONHR (R is unsubstituted or substituted alkyl or aryl);

$-CH_2-S-CH_2$-phenyl

When Cp-gly-Cp is combined with technetium, the following complex with the protecting groups removed is formed:



The preferred protecting group has the formula $-CH_2$-NHCOR wherein R is a lower alkyl having 1 and 8 carbon atoms, phenyl or phenyl-substituted with lower alkyl, hydroxyl, lower alkoxy, carboxy, or lower alkoxycarbonyl.

Compounds of the present invention can generally advantageously be

prepared on an amino acid synthesizer. Compounds of this invention are advantageous in that they are soluble and the sulfur is stabilized.

In forming the complex of radioactive technetium with the compounds of this invention, the technetium complex, a salt of technetium-99m pertechnetate, is reacted with the compound of this invention in the presence of a reducing agent such as stannous chloride ferrous ion or sodium dithionite. These technetium labeled complexes can also be made by exchange of a prereduced technetium -99m complex. The complexes are conveniently provided in a kit form comprising a sealed vial containing a predetermined quantity of a compound to be labeled and a sufficient amount of reducing agent to label the compound with technetium-99m. Alternatively, the complex may be formed by reacting the compound of this invention with a pre-formed labile complex of technetium and another compound. This process is known as ligand exchange, is well known to those skilled in the art, and the labile complex may be formed using such compounds as tartrate, citrate, gluconate or mannitol, for example. Among the technetium-99m pertechnetate salts are included the alkali metal salts such as the sodium salt or ammonium salts, or lower alkyl ammonium salts. The reaction of the compound of this invention with pertechnetate or preformed labile complex can be carried out in an aqueous medium at room temperature. The anionic complex which has a charge of -1 is formed in the aqueous medium in the form of a salt with a suitable cation such as sodium, ammonium cation, mono, di- or tri-lower alkyl amine cation, etc. Any conventional salt of the anionic complex with a pharmaceutically acceptable cation can be used in accordance with this invention.

In carrying out the reaction of the compounds of this invention with pertechnetate or a labile complex to form the anionic complex, the thiol protecting group is cleaved. Therefore, this reaction not only introduces the radioactive metal into the compound but also cleaves the thiol protecting group. All of the aforementioned thiol protecting groups are cleaved by a

reaction of salts of radioactive metals in accordance with this invention.

In forming the complex the radioactive material has a suitable amount of radioactivity. In forming the Tc-99m radioactive anionic complexes, it is generally preferred to form radioactive complexes in solutions containing radioactivity at concentrations of from about 0.01 milliCuries (mCi) to 100 mCi per ml.

The complex can be used for visualizing organs such as the kidney for diagnosing disorders in these organs, tumors and blood clots can also be imaged. In accordance with this invention, the anionic complex either as a complex or as a salt with a pharmaceutically acceptable cation is administered in a single unit injectable dose. Any of the common carriers such as sterile saline solution, plasma, etc., can be utilized after the radiolabeling for preparing the injectable solution to diagnostically image various organs, clots, tumors and the like in accordance with this invention. Generally, the unit dose to be administered has a radioactivity of about 0.01 mCi to about 100 mCi, preferably 1 mCi to 20 mCi. The solution to be injected at unit dosage is from about 0.01 ml to about 10 ml. After intravenous administration, imaging of the organ *in vivo* can take place in a matter of a few minutes. However, imaging can take place, if desired, in hours or even longer, after injecting into patients. In most instances, a sufficient amount of the administered dose will accumulate in the area to be imaged within about 0.1 of an hour to permit the taking of scintiphotos. Any conventional method of imaging for diagnostic purposes can be utilized in accordance with this invention.

The complexes may be administered intravenously in any conventional medium for intravenous injection such as an aqueous saline medium, or in blood plasma medium. Such medium may also contain conventional pharmaceutical adjunct materials such as, for example, pharmaceutically acceptable salts to adjust the osmotic pressure, buffers, preservatives and the like. Among the preferred mediums are normal saline and plasma.

The methods for making and labeling these compounds are more fully illustrated in the following examples.

Example 1

Cys(Acm)GlyCys(Acm)GlyGlyArgGlyAspSer

The title compound was prepared on a 0.25 millimole scale using an Applied Biosystems Model 431A peptide Synthesizer, N-terminus Fmoc protection and HMP resin (see Scheme). The product was cleaved from the resin using 95% trifluoroacetic acid at room temperature for 3 hours. Work-up and high performance liquid chromatography (HPLC) purification (using a Vydac 2.20cm x 25cm, 10um, C-18 column with a 20-minute gradient of 0.1% trifluoroacetic acid to 70% acetonitrile/ 0.1% trifluoroacetic acid at a flow rate of 25 ml/min) gave 50 mg of the title compound, 95% pure. (HPLC peak eluted at 5.5 min; Pos. ion FABMS Calc MM 952.97, Found 953).

Scheme for Preparation of the Title Compound

```
                FmocSer(tBu)
HMP R sin ------------> FmocSer(tBu) Resin
                 (a)

FmocAsp(OtBu)                                          FmocGly
------------> FmocAsp(OtBu)Ser(tBu) Resin ------------>
    (b)                                                  (b)

                                          FmocArg(Mtr)
FmocGlyAsp(OtBu)Ser(tBu) Resin ---------------->
                                              (b)

                                                    FmocGly
FmocArg(Mtr)GlyAsp(OtBu)Ser(tBu) Resin ---------------->
                                                      (b)

                                                     FmocGly
FmocGlyArg(Mtr)GlyAsp(OtBu)Ser(tBu) Resin ---------------->
                                                       (b)

                                                     FmocCys(Acm)
FmocGlyGlyArg(Mtr)GlyAsp(OtBu)Ser(tBu) Resin ---------------->
                                                         (b)

FmocCys(Acm)GlyGlyArg(Mtr)GlyAsp(OtBu)Ser(tBu) Resin

   FmocGly
---------------->
    (b)

FmocGlyCys(Acm)GlyGlyArg(Mtr)GlyAsp(OtBu)Ser(tBu) Resin

  FmocCys(Acm)
---------------->
      (b)

FmocCys(Acm)GlyCys(Acm)GlyGlyArg(Mtr)GlyAsp(OtBu)Ser(tBu)


Resin ---------------->
            (c)

Cys(Acm)GlyCys(Acm)GlyGlyArgGlyAspSer
```

(a) DCC, HOB, NMP
(b) 1.piperidine, NMP, 2. DCC, HOB, NMP
(c) 1.piperidine, NMP, 2. 95% CF_3CO_2H, 3. HPLC

DCC = dcyclohexylcarbodiimide
HOB = hydroxybenztriazole
NMP = N-methylpyrrolidinone
HMP = p-hydroxymethylphenoxymethylpolystyrene
Fm c = 9-flu renylmeth xycarbonyl
tBu = t rt-butyl
Mtr = 4-meth xy-2,3,6-trimethylbenzenesulfonyl
Acm = acetamidom thyl

Example 2

Radiolabeling of Compound of Example 1 with Tc-99m

0.3 mg of the compound prepared as in Example 1 was dissolved in 0.3 ml of 0.05M potassium phosphate buffer (pH 7.4) containing 0.5 mM EDTA. Tc-99m gluceptate was prepared by reconstituting a Glucoscan vial (E.I. DuPont de Nemours, Inc.) with 1.0 ml of Tc-99m sodium pertechnetate containing 26 mCi. After 15 minutes at room temperature, 75 ul of Tc-99m gluceptate was added to 0.3 mg of the compound prepared as in Example 1 and boiled for 45 minutes.

The extent of Tc-99m labeling of the peptide was determined by chomatography using Merck silica gel 60 F_{250} aluminum-backed strips which were spotted with 10 ul of sample and chromatographed with acetonitrile:0.5M sodium chloride solvent (15:85) approximately 2% of Tc-99m radioactivity remained at R_f 0.0, confirming that no significant Tc-99m colloids or aggregates were generated.

The Tc-99m labeled peptide purity was determined by HPLC using a Brownlee Spheri-5 (5um) resin, RP-18, 220 x 4.6 mm column and the following gradient: 0% A (CH_3CN:H_2O:TFA, 70:30:0.1) and 100% B (0.1% TFA in H_2O) to 100% A + 0% B over 10 minutes at 1.5 ml/min; and then held at the 100% A solvent for 5 minutes. This protocol yielded 100% of the radiometric species detected (by in-line NaI detector) as a single species (retention time = 10.9 min). Tc-99m gluceptate and Tc-99m sodium pentechnetate elute between 1 and 4 minutes under identical conditions, confirming the identity of the Tc-99m labeled peptide isolated.

What is claimed is:

1. A polypeptide for labeling with technetium-99m and imaging target sites within a mammalian body comprising:

(a) a specific binding polypeptide region which specifically binds to the target site to be imaged and

(b) a technetium binding region of the formula

Cp(aa)Cp

wherein Cp is a protected cysteine and (aa) is an amino acid and wherein the technetium binding region is covalently bound to the specific binding polypeptide region.

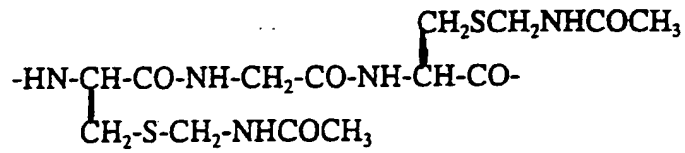
2. A polypeptide according to claim 1 wherein the specific binding polypeptide region and Cp(aa)Cp is covalently linked through one or more amino acids.

3. A polypeptide according to claim 1 wherein the protected cysteine has a protecting group of the formula

$-CH_2-NH-CO-R$

wherein R is a lower alkyl having 1 to 6 carbon atoms, phenyl, or phenyl substituted with lower alkyl, hydroxy, lower alkoxy, carboxy, or lower alkoxycarbonyl, or 2-,3-,4-pyridyl.

4. A polypeptide according to claim 1 wherein Cp(aa)Cp has the formula:



5. A polypeptide according to claim 1 wherein the specific

binding polypeptide region specifically binds to clots, tumors, sites of infection, atherosclerotic plaques, amyloid plaques or bone.

6. A polypeptide according to claim 1 wherein the specific binding polypeptide region is selected from polypeptides consisting of the amino acid sequences:

YRALVDTLK
RALVDTLK
RALVDTLKFVTQAEGAK
YAKFRETLEDTRDRMY
AKFRETLEDTRDRMY
YAALDLNAVANKIADFEL
AALDLNAVANKIADFEL
YRALVDTLKFVTEQAKGA
RALVDTLKFVTEQAKGA
YRALVDTEFKVKQEAGAK
RALVDTEFKVKQEAGAK
YRALVDTLKFVTQAEGAK
VGVAPGVGVAPGVGVAPG
VPGVGVPGVGVPGVGVPGVG
formyl.Nleu.LF.Nleu.YK
formyl MIFL
formyl MLFK
formyl MLFI
formyl MFIL
formyl MFLI
formyl MLIF
formyl MILF
TKPR
VGVAPG
formyl MLF
NDGDFEEIPEEYLQ
NDGDFEEIPEEY(SO_3Na)LQ
GPRG
D-Phe.PRPGGGGNGDFEEIPEEYL
RRRRRRRRRGDV
PLYKKIIKKLLES
RGD
RGDS
YIGSR
CH_2CO.YIGSRC
EKPLQNFTLSFR

7. The polypeptide of claim 6 bound to technetium-99m.

8. A complex formed by reacting a compound of claim 1 with technetium-99m in the presence of a reducing agent.

9. The complex of claim 8, wherein the said reducing agent is selected from the group of a dithionite ion, a stannous ion, or a ferrous ion.

10. A complex formed by labelling a compound of claim 1 with technetium-99m by ligand exchange of a prereduced technetium-99m complex.

11. A kit for preparing a radiopharmaceutical preparation, said kit comprising sealed vial containing a predetermined quantity of a compound of claim 1 and a sufficient amount of reducing agent to label said compound with technetium-99m.

12. A method for imaging a target site within a mammalian body comprising administering an effective diagnostic amount of a polypeptide of claim 1 which is labeled with technetium-99m and wherein the specific binding polypeptide region binds to the target site, and detecting the localized technetium-99m.

13. The process of preparing the peptide according to Claim 1 wherein the peptide is chemically synthesized *in vitro*.

14. The process of preparing the peptide according to Claim 13 wherein the peptide is synthesized by solid phase peptide synthesis.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 49/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	WO,A,9015818 (ANTISOMA LTD) 27 December 1990, see the whole document ---	1-14
Y	WO,A,9006323 (CENTOCOR INC.) 14 June 1990, see page 2, line 22 - page 4, line 6; page 8, lines 9-17; page 17, example 2; claims ---	1-14
Y	EP,A,0284071 (NEORX) 28 September 1988, see the whole document (cited in the application) ---	1-14
Y	EP,A,0137457 (E.I. DU PONT DE NEMOURS AND CO.) 17 April 1985, see the whol document ---	1-14
Y	EP,A,0055028 (MINNESOTA MINING AND MANUFACTURING CO.) 30 June 1982, see the whole document, especiaally page 16, lines 22-35 --- -/-	1-14

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09-06-1992	29. 07. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO,A,9010463 (NEORX) 20 September 1990, see the whole document	1-14
Y	J. Nucl. Med., vol. 31, no. 5, May 1990, (New York, US), L.C. KNIGHT et al.: "Thrombus imaging with TC-99M synthetic peptides reactive with activated platelets", page 757, abstract no. 209, see abstract (cited in the application)	1-14
P,Y	Chemical Abstracts, vol. 115, 1991, (Columbus, Ohio, US), B. LI et al.: "A new bifunctional chelating agent alpha,xi-N,N'-bis(L-cysteinyl)-L-lysine for radiolabeling of monoclonal antibodies with technetium-99M", see page 2001, abtract no. 159733f, & CHIN. CHEM. LETT. 1991, 2(4), 285-8, see abstract	1-14
A	Chemical Abstracts, vol. 114, 1991, (Columbus, Ohio, US), see page 850, abstract no. 186080b, & JP,A,02268197 (ICHIKAWA WOOLEN TEXTILE CO., LTD) 1 November 1990, see abstract	
A	EP,A,0108406 (F. HOFFMANN-LA ROCHE AND CO.) 16 May 1984, see claims (cited in the application)	

B x I Observations where certain claims were found unsearchable (Continuation of item 1 f first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [XX] Claims Nos.: PLEASE SEE REMARK!!!!
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a diagnostic method practised on the human/animal body the search has been carried out and based on the alleged effects of the compound / compositon.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9200757 SA 57367

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/07/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9015818	27-12-90	EP-A- 0429626	05-06-91
		GB-A- 2241243	28-08-91
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